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(54) Title: TREATMENT OF UPPER AIRWAY ALLERGIC RESPONSES WITH A COMBINATION OF HISTAMINE RECEPTOR ANTAGONISTS

(57) Abstract

Relief from the symptoms of rhinitis is obtained by treatment with: (a) an antihistaminic effective amount of a histamine H₁ receptor antagonist; together with (b) a sufficient amount of a histamine H₃ receptor antagonist to provide a nasal decongestant effect. The components may be administered together in a single dosage form, or separately in the same or different dosage forms to maintain therapeutic systemic levels of both components.

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10 TREATMENT OF UPPER AIRWAY ALLERGIC RESPONSES WITH A COMBINATION OF HIS-TAMINE RECEPTOR ANTAGONISTS

INTRODUCTION TO THE INVENTION

15

The present invention relates to a composition for treating allergy - induced responses in the mammalian airway, and to a method of treating allergy - induced airway responses.

20

Allergies are known to affect a very large fraction of the population. The allergic response in a particular individual may be caused by any of numerous environmental factors, some of which are consistently present and others being more seasonal in nature. Although not always recognized, worldwide losses in productivity due to allergic responses are economically very significant.

25

Clinical symptoms of seasonal allergic rhinitis typically include nasal itching and irritation, sneezing and watery rhinorrhea, frequently accompanied by nasal congestion. The perennial allergic rhinitis clinical symptoms are similar, except that nasal blockage may be more pronounced. Either type of allergic rhinitis may also cause other symptoms such as itching of the throat and/or eyes, epiphora and edema around the eyes. These symptoms may vary in intensity from

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the nuisance level to debilitating. Other types of rhinitis present the same types of symptoms.

At the cellular level, the mechanism of rhinitis has been the subject of considerable study. In addition to other processes, the 5 mechanism is well known to involve the release of histamine [2-(4-Imidazolyl) ethylamine] which is synthesized and stored in secretory granules of mast cells located throughout the body, such as the skin, lungs, gut and the lining of blood vessels. Mast cell histamine is a mediator in immediate hypersensitivity reactions. Following its 10 release from mast cells in the nasal mucosa, and acting primarily through histamine H₁ receptors, histamine evokes mucous secretion and vasodilatation, increases vascular permeability, induces pruritus and causes sneezing by sensory - nerve stimulation. The released histamine also can cause symptoms including hypotension, 15 tachycardia, flushing and headache. Although histamine H₂ receptors (which typically activate to increase gastric acid secretion) may also be involved in the allergic response, their effects are not presently considered to be significant.

Histamine H₃ receptors are found on sympathetic nerves, where 20 they modulate sympathetic neurotransmission and attenuate a variety of end organ responses under control of the sympathetic nervous system. Specifically, H₃ receptor activation by histamine attenuates nonepinephrine outflow to resistance and capacitance vessels, causing vasodilatation.

25 It is thought that the primary symptoms of rhinitis involve activity at H₁ receptors. Indeed, relief has been provided since the 1940's by a succession of "antihistamine" H₁ receptor antagonists including the well-known drug chlorpheniramine maleate. More recently developed drugs provide H₁ receptor antagonist activity with lower levels of 30 undesirable side effects, among the most noteworthy being greatly reduced incidences of somnolence and anticholinergic effects. This is considered to result from the later drugs' greater selectivity for H₁.

receptors, as well as their reduced ability to cross the blood-brain barrier. In general, none of the H₁ receptor antagonists are known to have significant effects on H₂ or H₃ receptors.

H₁ receptor antagonists have been proven efficacious for 5 preventing and relieving sneezing, itching, rhinorrhea and other symptoms of the early allergic response, but have not been found to be very effective for relief of the nasal blockage which is characteristic of the later stages of an allergic reaction. Thus, it has been common to concurrently administer sympathomimetic amine decongestant 10 drugs, such as phenylpropanolamine or pseudoephedrine which function as α -adrenoceptor agonists; several combination products containing both H₁ receptor antagonists and sympathomimetic amine decongestants are commercially available. However, not all allergy sufferers should use these decongestants drugs, due to their 15 frequently observed central nervous system and cardiovascular side effects which include agitation, sleeplessness, tachycardia, angina pectoris and hypertension.

U.S. Patents 5,217,986 and 5,352,707 to Pomponi et al. attribute 20 an ability for treating conditions including rhinitis and airway congestion to certain compounds apparently having H₃ receptor binding activity, but no H₁ receptor antagonist activity. However, no clinical observation or other support is provided for this proposition.

It would be desirable to have available a treatment for allergic 25 rhinitis which provides relief from all of the common symptoms thereof, including nasal congestion, but which does not exhibit adverse nervous system or cardiovascular effects.

SUMMARY OF THE INVENTION

30 The invention is a composition for the treatment of the symptoms of allergic rhinitis, comprising a combination of at least one histamine H₁ receptor antagonist and at least one histamine H₃ receptor

antagonist. Also included within the invention is a method for treating symptoms of allergic rhinitis, comprising maintaining in the circulatory system an antihistaminic amount of at least one histamine H₁ receptor antagonist, together with sufficient amounts of at least one histamine H₃ receptor antagonist to provide a nasal decongestant effect.

DETAILED DESCRIPTION OF THE INVENTION

10 For purposes of the present invention, an "antihistaminic" effect will be considered that symptomatic relief which has classically been considered as being obtainable by a sufferer of rhinitis, resulting from the administration of H₁ receptor antagonists, e.g., without limitation thereto, attenuation of sneezing, ocular and nasal itching, rhinorrhea 15 and epiphora. This antihistaminic effect specifically does not include significant relief from nasal congestion symptoms.

20 Numerous chemical substances are known to have histamine H₁ receptor antagonist activity. Many useful compounds can be classified as ethanolamines, ethylenediamines, alkylamines, phenothiazines or piperidines. Representative H₁ receptor antagonists include, without limitation: astemizole, azatadine, azelastine, acrivastine, brompheniramine, chlorpheniramine, clemastine, cyclizine, 25 carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine (also known as SCH-34117), doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, mizolastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, 30 picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine and triprolidine. Other compounds can readily be evaluated to determine activity at H₁ receptors by known methods, including specific blockade of the contractile response to histamine of isolated guinea pig ileum.

The currently known histamine H₃ receptor antagonists cannot be easily classified chemically, but include, without limitation: thioperamide, impromidine, burimamide, clobenpropit, impentamine, mifetidine, S-sopromidine, R-sopromidine, SKF-91486, GR-175737, 5 GT-2016, UCL-1199 and clozapine. Other compounds can readily be evaluated to determine activity at H₃ receptors by known methods, including the guinea pig brain membrane assay and the guinea pig neuronal ileum contraction assay, both of which are described in U.S. Patent 5,352,707. Another useful assay utilizes rat brain membranes 10 and is described by West et al., "Identification of Two H₃-Histamine Receptor Subtypes," *Molecular Pharmacology*, Vol. 38, pages 610-613 (1990).

A particularly useful screening assay measures binding to sites in guinea pig brain membranes. This test is described in detail by 15 Korte et al., "Characterization and Tissue Distribution of H₃ Histamine Receptors in Guinea Pigs by N^a -Methylhistamine," in *Biochemical and Biophysical Research Communications*, Vol. 168, pages 979-986 (1990), and quantifies the displacement of bound radiolabeled N^a -methylhistamine from tissues by candidate compounds. Results are 20 expressed as "K_i" values, in nanoMolar (nM) units, which values can be considered as being dissociation constants for the H₃ antagonist on the H₃ receptor system, or an index of antagonist affinity for the receptor. The present inventors have evidence that decongestant activity in their invention for a given H₃ antagonist concentration can be 25 predicted to increase as the K_i value obtained from the assay for an antagonist decreases. In general, K_i values less than about 200 nM are considered necessary for an agent to be useful as an H₃ antagonist in the invention. More preferably, the agent will exhibit K_i values of 100 nM or less.

30 Any of the foregoing drugs may be used in the form of a pharmaceutically suitable salt, ester or other form, where solubility or

other characteristics of the drug should desirably be modified, such as for formulation convenience.

While it is not desired to be bound to any particular theory of operation, it is normally expected that sympathetic innervation of airway blood vessels leads to vasoconstriction, which would oppose airway resistance and congestion. However, during conditions of mast cell activation and the release of histamine, such as in allergic diseases, the released histamine acts on H₃ receptors located on sympathetic nerve terminals to inhibit sympathetic neurotransmission and opposes the decongestant effect of norepinephrine, as well as activating H₁ receptors that produce other symptoms of allergic diseases.

Antihistamines that block H₁ receptors do not antagonize the H₃ receptor-mediated inhibition of norepinephrine release and, therefore, are generally without activity against the effects of histamine in promoting airflow limitation and congestion.

The decongestant effect of the combination of the present invention is thought to reside in the anti-H₃ activity which enhances the release of norepinephrine, a natural endogenous decongestant, at the site of congestion in the nose, but not elsewhere in the body, so no systemic cardiovascular effects are observed. The antiallergic effects reside primarily in the anti-H₁ activity of the treatment.

Amounts of H₁ receptor antagonists and H₃ receptor antagonists which are administered to achieve antihistaminic and decongestant effects will vary, depending on the activities of the exact compounds used. In general, between about 1 and about 1000 milligrams of each compound will be administered in a dose. The compounds may be combined in a single dosage formulation, or may be administered in separate dosage forms, and these may be solid (such as tablets, capsules, sachets and the like), liquid (such as solutions or suspensions) or inhalation aerosols for either or both compounds. While the solid compounds will typically be administered orally, the

liquids may be administered orally or by injection. Other dosage forms, such as suppositories, are also useful.

Appropriate amounts of the H₁ receptor antagonists and H₃ receptor antagonists for each dose, and the proper dosing regimen, 5 must be determined for each combination by suitable clinical trials. Ideally, each drug will have a similar duration of action after dosing, frequently indicated by elimination half-life and by clinical observation of symptom relief. However, in the event that the individual drug duration of action is considerably different for members of a given 10 combination, it will be necessary to resort to alternate formulation techniques, such as inhibiting the release kinetics of a component from the formulation to prolong its activity. These techniques are well known in the pharmaceutical formulation art. The least expensive dosing regimen, however, may involve separately administering the H₁, 15 and H₃ receptor antagonists, using dose frequencies and strengths as necessary to maintain therapeutic systemic levels of both agents.

The invention will be further described by means of the following examples, which are not intended to limit the scope of the claimed invention in any manner. In the examples, compositional percentages 20 are weight percentages, unless the context clearly indicates otherwise.

Example 1

25 An objective measurement of nasal airway resistance to air flow is used to demonstrate the induction and relief of nasal congestion.

Adult cats are anesthetized with intraperitoneal injections of sodium pentobarbital. The right femoral artery and vein are cannulated for measurement of blood pressure with a pressure 30 transducer, and for the administration of drugs. The animals are paralyzed with intravenous gallamine triethiodide and subsequently mechanically ventilated with room air, using an animal ventilator. After

isolation of the cervical esophagus, a cuffed endotracheal tube is advanced rostrally into the posterior nasopharynx and inflated to form an air-tight seal, allowing continuous measurement of pressure changes within the nasal cavity. The right nasal airway is occluded 5 with dental impression compound, and humidified air is passed through the left nasal airway at about 1.7 liters per minute. By means of pressure transducers, nasal airway pressure and insufflation pressure can be derived and electronically recorded.

10 Nasal airway resistance (NAR) is determined by dividing the pressure within the nasal cavity (expressed in centimeters of water) by the air flow rate (expressed in liters per minute). Measurements with 18 subject animals yield an average baseline NAR of 2.6.

15 The known histamine releaser "Compound 48/80" (the condensation product of N-methyl-p-methoxyphenethylamine with formaldehyde, sold by Sigma Chemical Company, St. Louis, Missouri, USA), as a 1.0 percent solution in 0.9 percent aqueous saline solution, is aerosolized into the air stream for 2 minutes to induce an increased NAR. This effect is used to study the decongestant effects 20 of various test substances, administered to the animals intravenously 10 minutes prior to the introduction of Compound 48/80. These substances include 0.9 percent aqueous saline (normal saline "Vehicle"), phenylpropanolamine hydrochloride at 1.0 mg/Kg of the free drug, thioperamide maleate at 10 mg/Kg of the free drug and chlorpheniramine maleate at 0.8 mg/Kg of the free drug, all of the drug 25 compounds being in solution in 0.9 percent aqueous saline.

Results are obtained, as shown below:

| | <u>Treatment</u> | <u>NAR</u> |
|----|---------------------|------------|
| | Vehicle | 9.1 |
| 30 | Thioperamide | 6.7 |
| | Chlorpheniramine | 6.0 |
| | Phenylpropanolamine | 2.9 |

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It can be seen that the sympathomimetic amine significantly prevents congestion, but the H₁ and H₃ receptor antagonists, administered singly, are decidedly inferior at preventing nasal congestion. Only the phenylpropanolamine gives a statistically different result from that for the vehicle.

5

Example 2

The experiment of the preceding example is repeated, but the 10 intravenous drugs are varying amounts of thioperamide (administered as the maleate), in solution together with a constant 0.8 mg/Kg of chlorpheniramine ("CPA," administered as the maleate).

Results are obtained, as shown below:

| 15 | <u>Treatment</u> | <u>NAR</u> |
|----|------------------------------|------------|
| | Vehicle | 9.1 |
| | Thioperamide 1.0 mg/Kg + CPA | 6.1 |
| | Thioperamide 3.0 mg/Kg + CPA | 4.3 |
| | Thioperamide 10 mg/Kg + CPA | 2.2 |

20

There is a significant congestion prevention response to increasing doses of thioperamide in the presence of chlorpheniramine, although the combination of 1 mg/Kg thioperamide and 0.8 mg/Kg chlorpheniramine is not statistically different from the vehicle. Comparison of the maximum response results shown in this 25 example, to the results in Example 1 for administration of 1.0 mg/Kg phenylpropanolamine, indicates that the combination of 0.8 mg/kg chlorpheniramine and 10 mg/Kg thioperamide is at least as effective at preventing nasal congestion.

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Example 3

The experiment of preceding Example 1 is repeated, but the intravenous drug administered is clobenpropit in varying amounts, 5 either alone or in solution together with a constant 0.8 mg/Kg of chlorpheniramine ("CPA," administered as the maleate).

Results are obtained, as shown below:

| | <u>Treatment</u> | <u>NAR</u> |
|----|------------------------------|------------|
| 10 | Vehicle | 9.1 |
| | Clobenpropit 1.0 mg/Kg | 8.5 |
| | Clobenpropit 0.3 mg/Kg + CPA | 2.9 |
| | Clobenpropit 1.0 mg/Kg + CPA | 3.4 |

15 Clobenpropit alone does not exhibit significant prevention of nasal congestion, but the combinations of clobenpropit and chlorpheniramine are effective to prevent congestion. The results for 0.3 and 1.0 mg/Kg clobenpropit, administered together with 0.8 mg/Kg chlorpheniramine, are statistically different from those for the vehicle.

20

Example 4

Blood pressure data from the experiments of the preceding examples are examined, to determine the effects of certain congestion 25 - preventing treatments. These data are as shown below, wherein the change from baseline is shown for various drugs ("CPA" being chlorpheniramine, administered as the maleate):

| | <u>Treatment</u> | <u>mm Hg</u> |
|----|---------------------------------------|--------------|
| 30 | Vehicle | - 16 |
| | Thioperamide 10 mg/Kg + CPA 0.8 mg/Kg | - 10 |
| | Phenylpropanolamine 1 mg/Kg | + 31 |

The data show that treatment with the thioperamide and chlorpheniramine combination has little adverse effect on blood pressure, while the phenylpropanolamine treatment (which yields an approximately equivalent nasal congestion - preventing effect) 5 significantly increases blood pressure. Only the results for phenylpropanolamine are statistically different from those for the vehicle.

Example 5

10

The affinity of various histamine H₃ receptor antagonists for binding sites is determined by a guinea pig brain membrane assay, according to the procedure of Korte et al., *Biochemical and Biophysical Research Communications*, Vol. 168, pages 979-986

15 (1990).

Results are as shown below:

| | <u>Compound</u> | <u>K_i, nM</u> |
|----|-----------------|--------------------------|
| | Verongamine | 280 |
| 20 | Thioperamide | 12 |
| | Clobenpropit | 0.1 |

These results predict that verongamine, having a K_i value higher than 200 nM, will not be useful in the practice of the invention.

25

To test the statement in U.S. Patent 5,217,986 that verongamine itself has decongestant activity, an experiment similar to that of preceding Example 1, but with a different vehicle, is conducted. The following results are obtained:

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| <u>Treatment</u> | <u>NAR</u> |
|----------------------|------------|
| Vehicle | 7.8 |
| Verongamine 10 mg/Kg | 7.3 |

5 Contrary to the prediction of the patent, the result for verongamine is not statistically different from that for the vehicle.

Example 6

10 The experiment of preceding Example 3 is conducted, using loratadine as the antihistaminic compound at 3 mg/Kg, administered in a solution ("Vehicle") which is 30 percent Dimethylsulfoxide, 40 percent Ethanol and 30 percent normal saline, and using thioperamide as the H₃ receptor antagonist at 10 mg/Kg.

15 Results are obtained, as follows:

| | <u>Treatment</u> | <u>NAR</u> |
|----|---------------------------|------------|
| | Vehicle | 12.6 |
| | Loratadine | 10.2 |
| 20 | Loratadine + Thioperamide | 2.1 |

Only the results for the combination of loratadine and thioperamide are statistically different from those for the vehicle.

25 Example 7

The experiment of the preceding example is repeated, using 1 mg/Kg descarboethoxyloratadine as the histamine H₁ antagonist. Similar results are obtained.

Example 8

Tablets containing a combination of H₁ receptor antagonist and H₃ receptor antagonist are prepared by combining the following 5 ingredients (per tablet to be prepared):

| | | |
|----|---------------------------|------------------|
| | H ₁ antagonist | effective amount |
| | H ₃ antagonist | effective amount |
| | Lactose | 100 mg |
| 10 | Corn starch, 10% paste | 5 mg |
| | Corn starch, dried | 25 mg |
| | Magnesium stearate | 1.25 mg |

The first, second, third, and a portion of the fifth, ingredients are 15 thoroughly blended in a suitable mixer for at least 10-15 minutes. The mixture is granulated with the fourth ingredient and, if necessary, passed through a sieve having openings about 0.6 mm. After drying, the granules are mixed with the sixth ingredient and the remaining portion of the fifth ingredient in a mixer until uniform and compressed 20 into tablets of a desired shape in a tablet press, using suitable dies. If desired, the tablets may be coated, such as with sugar and/or with a wax.

Example 9

25 Capsules containing a combination of H₁ receptor antagonist and H₃ receptor antagonist are prepared by combining the following ingredients (per capsule to be prepared):

| | | |
|----|---------------------------|------------------|
| 30 | H ₁ antagonist | effective amount |
| | H ₃ antagonist | effective amount |
| | Lactose | 125 mg |

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| | |
|--------------------|--------|
| Corn starch, dried | 25 mg |
| Magnesium stearate | 2.5 mg |

5 The first four ingredients are mixed thoroughly in a suitable mixer
for 10-15 minutes, then the fifth ingredient is added and mixing
continued for another 5 minutes. Predetermined amounts of the
mixture are filled into two-piece hard gelatin capsules of appropriate
size.

10

Example 10

15 A parenteral solution formulation is prepared by dissolving
effective amounts of the H₁ receptor antagonist and H₃ receptor
antagonist sterile powders in sterile water for injection, U.S.P. or
bacteriostatic water for injection, U.S.P. Suitable pH buffers and/or
preservatives may be added, as needed.

Example 11

20 An oral liquid is prepared by dissolving and/or suspending
effective amounts of an H₁ receptor antagonist and an H₃ receptor
antagonist in a solution made from water, containing desired
amounts of the following safely ingestible ingredients: sweetening
agents, flavorants, colorants, vegetable oil and suspending agents
25 and/or thickeners.

30 It should be noted that, in any of the formulations of preceding
Examples 8-11, either of the H₁ receptor antagonist or the H₃ receptor
antagonist can be omitted if the active compounds are to be
separately administered. It is not necessary to administer the drugs
in the same dosage forms.

WHAT IS CLAIMED IS:

1. A composition comprising: (a) an antihistaminic effective amount of a histamine H₁ receptor antagonist; and (b) a sufficient amount of a histamine H₃ receptor antagonist to provide a nasal decongestant effect; in a pharmaceutically acceptable carrier.
5
2. The composition of claim 1, wherein the components are combined into a solid dosage form.
10
3. The composition of claim 1, wherein the components are combined into a liquid dosage form.
15
4. The composition of claim 1, wherein the histamine H₁ receptor antagonist is selected from the group consisting of astemizole, azatadine, azelastine, acrivastine, brompheniramine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carboxamine, descarboethoxyloratadine, doxylamine, diphenhydramine, cetirizine, dimenhydrinate, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, 20 levocabastine, mizolastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripeleannamine, temelastine, trimeprazine, triprolidine and mixtures of any two or more of the foregoing.
25
5. The composition of claim 1, wherein the histamine H₃ receptor antagonist is selected from the group consisting of thioperamide, impromidine, burimamide, clobenpropit, impentamine, mifetidine, S-sopromidine, R-sopromidine, SKF-91486, GR-175737, 30 GT-2016, UCL-1199, clozapine and mixtures of any two or more of the foregoing.

6. The composition of claim 1, wherein the histamine H₁ receptor comprises loratadine.

7. The composition of claim 1, wherein the histamine H₁ receptor comprises descarboethoxyloratadine.

8. A method of relieving symptoms of rhinitis in a mammal, comprising simultaneously maintaining in the circulatory system: (a) an antihistaminic effect amount of a histamine H₁ receptor antagonist; and (b) a sufficient amount of a histamine H₃ receptor antagonist to provide a nasal decongestant effect.

9. The method of claim 6, wherein the H₁ receptor antagonist and the H₃ receptor antagonist are present in a single dosage form.

10. The method of claim 6, wherein the H₁ receptor antagonist and the H₃ receptor antagonist are administered in separate dosage forms.

11. The method of claim 6, wherein the histamine H₁ receptor antagonist is selected from the group consisting of astemizole, azatadine, azelastine, acrivastine, brompheniramine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carboxamine, descarboethoxyloratadine, doxylamine, diphenhydramine, cetirizine, dimenhydrinate, dimethindene, ebastine, epinastine, eflazagiline, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, mizolastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripeleannamine, temelastine, trimeprazine, triprolidine and mixtures of any two or more of the foregoing.

12. The method of claim 6, wherein the histamine H₃ receptor antagonist is selected from the group consisting of thioperamide, impromidine, burimamide, clobenpropit, impentamine, mifetidine, S-sopromidine, R-sopromidine, SKF-91486, GR-175737, GT-2016, 5 UCL-1199, clozapine and mixtures of any two or more of the foregoing.

13. The method of claim 6, wherein the histamine H₁ receptor comprises loratadine.

10 14. The method of claim 6, wherein the histamine H₁ receptor comprises descarboethoxyloratadine.

15. The method of claim 6, wherein the histamine H₃ receptor has a K_i value at least 200 nanoMolar.

15 16. The method of claim 6, wherein the histamine H₃ receptor has a K_i value at least 100 nanoMolar.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/13903

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/44 A61K31/55 A61K31/445 A61K31/415 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| X | MISAWA, TAKANO: "PHARMACOLOGICAL STUDIES ON THE RESPIRATORY TRACT: THE EFFECTS OF HISTAMINE RECEPTOR ANTAGONISTS ON GUINEA PIG RHINITIS MODEL" JAPANESE JOURNAL OF PHARMACOLOGY, vol. 64, no. S1, 1994, page P252 XP002042694 see the whole document --- | 1,4,5,8, 10-12 |
| X | WO 94 18961 A (UNIV MANITOBA) 1 September 1994 see page 7; claims 1,10,13,15,16 --- | 1,4-6 -/- |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

V document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

S document member of the same patent family

1

Date of the actual completion of the international search

Date of mailing of the international search report

7 October 1997

28.10.97

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Authorized officer

Kanbier, D

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 97/13903

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | SAKAI ET AL: "EFFECTS OF THIOPERAMIDE, A HISTAMINE H3 RECEPTOR ANTAGONIST, ON LOCOMOTOR ACTIVITY AND BRAIN HISTAMINE CONTENT IN MAST CELL-DEFICIENT W/W MICE" LIFE SCIENCES, vol. 48, 1991, pages 2397-2404, XP002042695 see page 2397; table 2 | 1,4,5 |
| X | GB 2 207 865 A (BIOGAL GYOGYSZERGYAR) 15 February 1989 see page 6, paragraph 2; example 2 see page 7, paragraph 2; claims 1,11,21 see page 7, paragraph 5 | 1,4,5 |
| A | MATSON ET AL: "An experimental non-invasive animal technique for measuring nasal airway resistance: I. Adrenergic and antihistaminic agents" ARCH. INT. PHARMACODYN. THER., vol. 232, no. 1, 1978, pages 68-78, XP002042696 see page 76; figures 5,6; table 1 | 1,4,5,8, 11,12 |
| A | US 5 019 591 A (GARDNER T W ET AL) 28 May 1991 see column 2, line 28-64; claims 1-3 | 1-5,8-12 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/13903

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 8-16 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Search Application No

PCT/US 97/13903

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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